IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY
CIVIL NO. 13-CV-4507(CCC)

IN RE: DEPOMED PATENT LITIGATION

TRANSCRIPT OF
PROCEEDINGS
(Public)

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Newark, New Jersey
March 15, 2016

B E F O R E:

THE HONORABLE CLAIRE C. CECCHI,
United States District Judge

Pursuant to Section 753 Title 28 United States Code, the following transcript is certified to be an accurate record as taken stenographically in the above-entitled proceedings.

S/Yvonne Davion
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Official Court Reporter

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W I T N E S S E S

Michelle Brown

Cross examination by Mr. Connolly

Cross examination by Mr. Aly

Redirect examination by Mr. Sitzman

Recross examination by Mr. Capuano

Further Redirect examination by Mr. Sitzman

Jonathan Steed

Direct examination by Mr. Harp

THE COURT: Good morning.

We have everyone on the record. Before we start, this is sealed, is it not?

MR. CONNOLLY: Your Honor, this first portion will be unsealed I'm guessing for about ten minutes.

THE COURT: That sounds fine.

MR. CONNOLLY: I will inform the Court when I believe there's a need to seal.

THE COURT: Very well.

M I C H E L L E B R O W N, previously sworn, resumes.

THE COURT: I remind you, Dr. Brown, that you remain under oath. Thank you.

CROSS EXAMINATION BY MR. CONNOLLY:

Q. Good morning, Dr. Brown.

A. Good morning.

Q. Nice to see you again. I don't know if you remember but my name is Terry Connolly and I represent the Roxane defendant in this action.

A. Yes.

Q. You've testified as an expert witness on behalf of Depomed before, right?

A. Yes.

Q. And the drug that was introduced in that trial was a drug called Gralise, right?

A. Yes.

Q. That was a long lasting version of the drug known as Gabapentin, right?
A. Yes.
Q. And Gralise is indicated for the management of postherpetic neuralgia, right?
A. Yes.
Q. And is postherpetic neuralgia sometimes referred as PHN?
A. Yes, it is.
Q. I'm going to use the acronym because I am going to stumble over the longer version. Is that fair?
A. Yes.
Q. Is PHN sometime, I'm sorry. Strike that.
Is PHN a neuropathic pain?
A. Primarily, yes.
Q. And you testified yesterday I believe that some forms of PHN can be monopathic, right?
A. Yes, it's usually polyneuropathic but it can be mononeuropathic.
Q. So, the answer to my question is it can sometimes be monopathic is yes? Is that correct?
A. It can sometimes be mononeuropathic.
Q. Thank you. In the Gralise trial you testified on behalf of Depomed that there was a long felt need for Depomed's Gralise product, right?

A. Yes.

Q. Now you were also a member of Depomed's speakers bureau, correct?

A. Yes.

Q. And the Depomed's speakers bureau is a group of clinicians who educate other practitioners about a particular drug that Depomed markets, right?

A. Yes.

Q. And one of your, I'm sorry, one of your responsibilities as a member of Depomed's speakers bureau is to teach other physicians about Depomed's Nucynta products and Gralise, right?

A. Including Gralise, yes.

Q. Okay. And when you meet with physicians -- let me strike that.

When you talk about your responsibilities as teaching physicians about Nucynta products, that would include both Nucynta IR and Nucynta ER, correct?

A. Yes.

Q. Now, when you meet with physicians as part of your work for Depomed's speakers bureau, you generally meet with doctors one at a time often in a physician or practitioner's office, correct?

A. That is correct. And sometimes it's in a lecture situation at a conference, for example.

Q. Okay. And you set up these meetings together with one or more of Depomed's sales representatives, right?

A. The sales representative set it up and I attend.

Q. Okay. And those sales representatives are Depomed employees whose job it is to sell Depomed's Nucynta, Gralise products, right?

A. In a simplified manner, yes.

Q. And when you meet with doctors as part of Depomed's speakers bureau, Depomed's sales representatives are there with you 90 percent of the time or more, right?

A. At least 90 percent, if not always.

Q. During those meetings that you have with the doctors to talk about Depomed's product, the sales representatives usually put out Depomed promotional materials, right?

A. They can, yes. I'm not involved with that part of it.

Q. Okay. Do you have before you a binder, a spiral bound? Would you pick that up, please? That's a copy of your deposition transcript?

A. Yes.

Q. Okay.

THE COURT: You know what, I'm sorry, when did this off the record but just so we can do it on the record, any issues with respect to the exhibits or the demonstratives?

MR. SITZMAN: No, your Honor.

THE COURT: Thank you.

Q. I'm going to ask you to turn to Page 242. Tell me when you're there.
A. Yes.
Q. And Lines 6 through 9.
A. Yes.
Q. You were asked the question, Well, what does the sales representatives do at meetings. And you answered They may put out any promotional materials that they have, right?
A. Yes.
Q. Now, during these meetings that you have as part of Depomed's speakers bureau, you present what is in the Nucynta or Nucynta ER labels, right?
A. When I'm speaking about Nucynta, yes.
Q. Right. So every time you speak about Nucynta IR, you present what is in the Nucynta IR label, right?
A. I'm obligated to speak about what's in the label, yes.
Q. And the same is true with respect to Nucynta ER. When you're presenting in these sales meetings, you refer to the label, right, for Nucynta ER?
A. I do.
Q. Right. Now you get paid by Depomed for your work as part of Depomed's speakers bureau.
A. I do because I take time from my practice to do that.
Q. Is the answer to my question yes, ma'am, doctor?
A. I said yes, I do.

Q. And your current rate for that work is between $1,000 and $3,000 per day, right?

A. Yes.

Q. And you also get reimbursed for your travel and any out of pocket expense, right?

A. Yes, I do.

Q. And you became a member of Depomed's speakers bureau in 2012 to the best of your recollection, right?

A. To the best of my recollection, yes.

Q. You estimate that you got paid about $50,000 last year by Depomed for your work on the Depomed speakers bureau, right?

A. I think I said that on average I think I get paid around $50,000 but I don't keep track of it very well.

Q. Okay. And you estimate that you got paid by Depomed about $50,000 per year for your work on Depomed's speakers bureau in each of the years of 2012, 2013, 2014 and 2015, right?

A. On average.

Q. So, your best estimate of the total amount of the compensation that you received from Depomed for meeting with doctors over the years 2012, 2013, 2014 and 2015 to tell them about Depomed's products was about $200,000. Was that correct?

A. About that based on that average, yes.

Q. Not just based on my average. I want your best recollection, doctor.

Is your best recollection that you've been paid approximately $200,000 in those four years for your work on the speakers bureau?

A. Yes.

Q. And that $200,000 that you got paid by Depomed does hot take into account the money that Depomed reimbursed you for the expenses that you incurred, right?

A. I can't really say. It may or may not.

Q. Okay. I'm going to ask you to turn to your deposition, ma'am, doctor. Please turn to Page 245.

A. Excuse me. Someone was coughing. 240 what?

Q. 245. Please tell me when you're there.

A. I am.

THE COURT: Hold off one second. We're just going to shut the ski lights so we can see this much better.

Q. So, do you have Page 245 before you, Dr. Brown?

A. Yes.

Q. Okay. I'm going to ask you to focus on the line starting on line four, okay? Going down to about 18. Okay?

So, there's a question which says "So, what are your estimates for 2012 and 2013?

"Answer: Probably similar, although they may be less for the earlier years.

"Question: Okay. But, sitting here today, your best estimate in terms of the compensation that you received from Depomed in connection with being a participant in their speakers bureau is roughly in the order of $200,000.

Is that correct?

"Answer: For four years.

"Question: That's correct.

"Answer: And I'm not including any reimbursement because that's money that I put out myself".

Do you see that?

A. Yes.

Q. Did I read that accurately?

A. You did.

Q. Now, you're still a member of Depomed's speakers bureau, right?

A. Yes.

Q. So, you've continued to work for Depomed as part of its speakers bureau and attend meetings with physicians and Depomed sales representatives to talk about Nucynta products during the course of your acting as an expert witness for Depomed in this case, right?

A. Yes, I have.

Q. And you continue to tell doctors at these meetings about Nucynta IR and Nucynta ER, right?

A. Yes, I do.

Q. And during your deposition in the beginning of February you told me that you had a meeting with doctors just the month before in January 2016 as part of your work on Depomed's speakers bureau, right?

A. Yes.

Q. Have you had any further meetings as part of Depomed's speakers bureau since January of this year?

A. Yes.

Q. How many?

A. I think one because I did one about a week or two ago.

Q. Okay. And were you paid approximately one -- how much were you paid for that?

A. $2,000.

Q. And do you plan to continue to work as part of Depomed's speakers bureau for the rest of this year?

A. Yes. It's something I enjoy quite a bit because I can educate people, which I'm no longer in academics, so, it gives me the opportunity to do it and I can engage with my colleagues.

Q. So, the answer to my question is yes, doctor?

A. The answer is yes.

Q. Doctor, if your lawyer wants to ask you to expound on any of the answers, he will be given that opportunity. I'm just going to ask you to try to answer my question so we can get through this as promptly as possible. Okay?

A. I will do the best I can.

Q. Thank you. And I'll try to do the same.

At that last meeting did you speak about Nucynta or Nucynta ER?

A. I spoke about Nucynta ER.

Q. Okay. And in terms of your enjoyment of in working for the Nucynta speakers bureau, you have no intention of resigning from that work, sitting here today, right?

A. Not at this time.

Q. So, you could be doing that for the next five years, right?

A. Conceivably, yes.

Q. You could conceivably be doing it for the next ten years, right?

MR. SITZMAN: Objection, your Honor. I'm trying to see the relevance here. We've gotten a little bit off field.

MR. CONNOLLY: Your Honor, she's being paid to talk about the product at issue in this litigation. It's clearly relevant.

THE COURT: How many questions along this line?

MR. CONNOLLY: I have about -- I'll withdraw the question about ten years. Okay.

MR. SITZMAN: Thank you.

THE COURT: Okay.

Q. You've also been a member of one of Depomed's drug advisory boards, right?

A. Yes.

Q. And your work on that drug advisory board involved meeting with other physicians together with representatives of Depomed to discuss Depomed's products, right?

A. Yes.

Q. And at that time, I'm sorry, before you became a member of Depomed's speakers bureau, you were also a member of Janssen's speakers bureau, right?

A. Yes and I did very little work with them.

Q. And at that time Nucynta was a product that was marketed in the United States by Janssen, right?

A. Yes.

Q. And in that capacity you also talked to other doctors about what was then Janssen's Nucynta product, right?

A. A few times, yes.

Q. And you understand that Janssen was once a plaintiff in this case, right?

A. Yes.

Q. And your work on the Janssen speakers bureau was similar to your work on the Depomed speakers bureau that you've just testified about, right?

A. Yes, although at the time I think Nucynta ER was not introduced and on the cusp of being introduced.

Q. When you're telling doctors about Nucynta ER, you discuss the clinical study section of the Nucynta ER label, right?

A. I do.

Q. Okay. And that label contains -- that label doesn't contain the actual studies themselves, right?

A. I don't agree with that because the label does include the studies.

Q. Okay. Doesn't the label include a high level summary of the study instead of the actual study itself?

A. It includes a summary approved by the FDA.

Q. Right. So I'll ask the question again.

So, the label does not contain the actual studies, just a summary, right?

A. Yes.

Q. Okay. Now, you've actually read the underlying studies that are summarized in the Nucynta ER label, right?

A. I have. As a clinician, I would have to.

Q. You actually have read the underlying study and not just the summary, correct?

A. I have read the studies.

Q. So, it's fair to say, Dr. Brown, that you are extremely knowledgeable about Nucynta ER, right?

A. I'm knowledgeable because I'm a good clinician and also because of the speakers bureau, yes.

Q. And you are not just knowledgeable, you are very knowledgeable, right?

A. I don't think I'm anymore knowledgeable than any clinician that I would expect to be, other than the fact that I have discussed it on a regular basis with other clinicians and conferred with them about their knowledge base.

Q. Now, you said that you don't think you're anymore knowledgeable than any other clinician. But, the whole purpose of these meetings that you've described is to teach the physicians about the product, right?

A. Yes. And part of that is based on my experience in using it, yes.

Q. Right. And if they knew as much about Nucynta ER as you did, there would be no need for you to meet them to teach them about the product, right?

A. I am also a specialist in pain management so in comparison to a family practitioner, for example, I know quite a bit more about pain management as well as the medications that we use to treat chronic pain.

Q. So, it's fair to say that you have greater knowledge about the Nucynta ER than most of the healthcare providers that you meet with as part of your work on Janssen's, strike that, on Depomed's speakers bureau ?

Let me see if I can withdraw the question and actually speak English this time.

Is it fair to say that you have greater knowledge about Nucynta ER than most of the healthcare providers that you meet with as part of the Depomed's speakers bureau, correct?

A. Again I think that's fair, but it's also based on the fact that I'm a specialist.

MR. CONNOLLY: Your Honor, I think we have come to the point in the proceedings where we are going to get to confidential information. And on behalf of Roxane, we request that you seal the courtroom.

THE COURT: I don't believe there's any objection to that, is there?

MR. SITZMAN: No objection, your Honor.

THE COURT: Any objection?

MR.FITZPATRICK: No.

THE COURT: All right. Let us seal the courtroom now.

(Whereupon the following testimony is under seal).

THE COURT: As I've been doing in the past, I'll just do this very quickly. Let's make sure whoever is in the room is supposed to be in the room.

Let's see, Depomed, Grunenthal, Actavis, Roxane Alkem. All right. Anyone who should not be here. Does anyone see anyone? No. All right. Remain seated. The transcript is sealed and the courtroom is sealed.

You may proceed.

(Whereupon the hearing was sealed)*.

(Lunch recess).

(Whereupon the following takes place in open court)*

THE COURT: All right. We are back. We are not under seal at this point. Is that correct?

MR.FITZPATRICK: That's correct, your Honor.

THE COURT: And the courtroom is open then. So, who is going to call the next witness? I know we have two witnesses.

MR. FITZPATRICK: I think our understanding is the plaintiffs are now resting on their case.

MR. GLANDORF: That is correct.

THE COURT: And that is on infringement. And when Dr. Brown comes back, it will be on a separate issue?

MR. GLANDORF: On validity, that's correct.

THE COURT: Very well. Thank you.

MR.FITZPATRICK: That being so, Actavis now wishes to move for judgment on partial findings under Rule 52(c) as to the plaintiff's claim of infringement of the '130 patent. In making argument on that, your Honor, I am afraid to ask that the courtroom be closed.

THE COURT: Fair enough. Let us close the courtroom again.

(Whereupon the hearing is under seal). *

(Whereupon the following takes place in open court).

THE COURT: I will be speaking to you in the next few days as to how to handle this, whether we want to take additional briefing and include it within our trial briefs, whether you want to do something before that time and have it done separately. Let me think about it a little bit. And I know the issues unfold every day obviously. And I appreciate the presentations today.

MR. FITZPATRICK: May I make one suggestion to think about in that regard, your Honor? I think and I assume that the post trial submissions will be findings of fact and conclusions of law.

THE COURT: We also require a trial brief as well.

MR.FITZPATRICK: Fair enough. Okay.

THE COURT: We might want to think about including that within the issue or there are many ways to deal with it. But, no, I definitely need a trial brief and findings of facts and conclusions of law proposed obviously.

Thanks so much. Thank you.

MR. SITZMAN: Thank you, your Honor.

MR.FITZPATRICK: Thank you, your Honor.

(Whereupon a short recess was taken.)

THE COURT: So, let me just reiterate where we

were. I heard application from all three defendants and applications from the plaintiffs pursuant to Rule 52 seeking judgment at this time.

As I've indicated, I am reserving on those applications. And I'll talk to the parties later about how to proceed on them. All right.

So, at this point is there anything further before we go to the next witness? Anything? Any other issues? All right.

J O N A T H A N S T E E D, sworn and testifies as follows:

DIRECT EXAMINATION BY MR. HARP:

THE COURT: Let's have counsel take a look at the exhibits unless you've done that during the break.

MS. RANNEY: Yes, we have. Christine Ranney for plaintiff Depomed.

Your Honor, we've previously lodged a foundation objection to defendant's Exhibit 1097 that was in the context of another witness. A foundation was not established at the deposition.

THE COURT: Which one is that?

MS. RANNEY: Defendant's exhibit, it's document title BN 200 hydrochloride.

THE COURT: All right. That was in the context of which witness?

MS. RANNEY: Dr. Michael Gruss. So the document

wasn't ultimately used. So plaintiffs would just like to renew our objection.

THE COURT: With respect to this document at this point we have another witness here. To the extent a proper foundation can be laid, I think we can proceed. But, otherwise we can deal with the issue as an issue arises.

How does that sound?

MS. RANNEY: Sure. That's fine, your Honor.

THE COURT: Any other issues with respect to any of the other documents?

MS. RANNEY: No. Thank you.

THE COURT: You may begin.

MR. HARP: Thank you, your Honor.

Q. Good afternoon, Professor Steed. Would you please state your name for the record?

A. It's Jonathan Steed.

Q. And what is the area in which you are offering opinions today, Professor Steed?

A. It's the invalidity of the '364 patent from the point of view of polymorphism.

Q. And were you with us here in the courtroom last week?

A. Yes, I was.

Q. And what portions of the trial did you observe?

A. I observed the testimony of Dr. Buschmann and Dr. Gruss.

Q. Were you here for opening statements as well?
A. Yes, I was.
Q. What is your current occupation?
A. I'm Professor of Chemistry at Durham University in the United Kingdom.
Q. What can you tell us about the chemistry department at Durham University?
A. We are very proud of Durham in terms of the complete university guide. We rank second after Cambridge and before Oxford.
We were number one for impact for our research in the U.K. and in the last research assessment exercise within Germany we do a good job.
Q. Is there a particular area of chemistry on which you have focused?
A. My research is generally on chemical synthesis, on crystallization, development of new crystallization technologies. So I have interest in studying of crystallization, other crystallization methods using gels, for example, solid form of organic and for that matter coordination of inorganic compounds and the technique used to study solid states in organic and inorganic compounds.
Q. You mentioned solid state compounds in your answer.
What do you mean by solid state chemistry and solid state compounds?

A. Yes, solid state as in crystals and crystalline forms as opposed to liquids and gases, for example.

Q. And you also have -- what is your experience with synthetic chemistry?

A. Yes, we make the compounds that we study in my lab. Our primary focus is on the solid state form and then crystallization. But, we have to make them first before we can study them.

Q. For the '364 patent, what is the area of technology to which that patent is directed?

A. That's a patent that is directed to a particular crystalline form of Tapentadol hydrochloride in this case.

Q. Where did you attend college?

A. I got my undergraduate and doctoral degrees from University College, London.

Q. I'm sorry, and your Ph.D. was also from?

A. University College, London, yeah.

Q. What was the subject of your Ph.D. research?

A. It was synthesis of methyl organic compounds and they are studied by techniques which is crystallography which I actually used to study that crystalline form.

Q. What did you do after completing your Ph.D. research?

A. Then I went on to do a NATO post doctoral fellowship at the Universities of Alabama and Missouri.

Then I was interested in again x-ray crystallography

and specifically the area of super molecular chemistry which is the area in which one molecule interacts with another one such as in crystals.

Q. And what did you do after your NATO fellowship ended?

A. Then I was appointed to a permanent position as an academic. We call that lecturer. It's equivalent to assistant Professor in the U.S. That was at Kings College, London. And I was there from 1995 through to the end of 2003.

Q. And what happened in 2003? Where did you go?

A. Then I moved to Durham University as a reader initially and now full Professor of Chemistry.

Q. What has been the nature of your work at Durham?

A. Yes, it's predominantly been, as I've described, the synthesis and crystallization of organic and molecular compounds and the study of their solid state form. And also the study of solids that are related to crystals such as gels.

Q. You mentioned determining the solid state structure of compounds.

Is that referred to as crystallography?

A. Yes, crystallography is a main technique but also a related range of other techniques that they use to study organic solids, thing likes differential scaling calorimetry, x-rays of single crystalline powder, x-ray crystallography, infrared spectroscopy and a whole range of other techniques.

Q. Do you publish papers as part of your research?

A. Absolutely.
Q. How many papers have you published?
A. Well over 300 now.
Q. How about books or book chapters?
A. Yes, a large range of book chapters. I'm also the author of a book in 2000 called Super Molecular Chemistry which talks about the way in which one molecule interacts with another in a variety of contexts, especially solid state chemistry. That was translated into Russian and Chinese and the second edition came out in 2009.

I'm editor of an 8-volume series entitled Super Molecular Chemistry from Molecules and other materials, again focusing upon the interactions of one molecule with another. There's a couple of other books that I have done in the early years as well that are on similar sorts of subjects.

Q. How often are your papers cited by other academic scientists?
A. Academics love to count these things. My work has been cited about 10,000 times or so.
Q. How does that compare to others in your field?
A. I guess that would put me in the top one percent or so.
Q. Do you also teach, as part of your job at Durham?
A. Most certainly.
Q. What courses do you teach?
A. At the moment I teach a core subject which is actually

Inorganic Chemistry. And I also teach Super Molecular Chemistry for advanced students. And over the years I've taught a very wide variety of subjects including crystallography of course, things like green chemistry, foundational chemistry. A variety of other techniques.

Q. And do you have a research lab at Durham?

A. Yes, I do.

Q. How many researchers do you have in your lab?

A. It varies according to the funding, of course. But, typically between 5 and 15.

Q. Have you been selected for any awards during your career as a chemist?

A. Yes, I have been quite lucky. I was awarded the 2010 called a Morgan Prize for my work in super molecular chemistry. That's a national award in the U.K.

Much earlier I won the 1998 Meldola (ph) medal, an international award for my work in the super molecular chemistry area. I was also particularly pleased to win the 2008 I think the vice chancellor award for excellence in doctoral supervision. So actually I am teaching my doctoral students how to do research which is perhaps the most important thing we do.

Q. Any awards related to your Ph.D. research?

A. Yes. I also won the Ramsey Medal for my Ph.D. which was the best Ph.D. in chemistry from the University College

London in my year.

Q. Does your research relate at all to the area of pharmaceuticals?

A. Yes, it does. One of the main thrusts of our research is to try and develop new ways to crystallize pharmaceuticals. This is the gel phase work that I mentioned.

Q. Could you describe a little bit this gel phase technology?

A. Yes. Within this context of pharmaceuticals, polymorph screening that the pharmaceutical companies do routinely, I am trying to develop new techniques for them to use within the screening methodology, perhaps things they may not have thought of before.

Q. And these gel techniques are new?

A. Yes, they are developed in my lab.

Q. When did you develop them?

A. The first publication in the pharmaceutical gel crystallization area was 2010 in the nature of chemistry.

Q. How did these gel methods compare to more routine crystallization techniques?

A. They are still very experimental. But what we hope is that they will offer a way of discovering new polymorphs that aren't easily found otherwise.

Q. And do you consult directly with the pharmaceutical industry?

A. Yes, I consult and collaborate with a variety of different companies within the pharmaceutical industry either through their sponsorship of students or through direct consultancy or of course expert witness work.

Q. And do you have experience related to crystal structures in pharmaceuticals as part of your work with the pharmaceutical industry?

A. Yes, absolutely. Crystal structures are like bread and butter if you like. We get crystal structures all the time.

Q. Have you consulted with brand name companies?

A. Yes, I have had students sponsored by JSK in the past. At the moment I am signing a deal with Astra Zeneca to sponsor a student as well to carry out research in pharmaceutical crystallization. I have done some consulting work with smaller brand name companies as well.

MR. HARP: Your Honor, at this point I would like to offer Professor Steed as an expert in chemistry and crystallography.

THE COURT: Any issue? Any objection?

MS. RANNEY: No issue, your Honor.

THE COURT: All right. He is so admitted as an expert in that field.

Q. Professor Steed, can I ask you to turn to DTX 304 please in your book? And we have it up on the screen as well.

What is this document?

A. So, this is the '364 patent which is directed to particular crystalline form, form A of Tapentadol hydrochloride.

Q. Does the '364 patent cover the Tapentadol molecule itself?

A. No, no, it's not directed to the synthesis or the molecule itself just one particular crystal form.

Q. Are you aware of any other patents that cover the molecule?

A. Yes, I believe the molecule is covered by the '737 patent.

Q. And does the '737 patent identify the crystal structure of Tapentadol?

A. No, it merely states that it crystallizes out and gives a melting point. But, otherwise doesn't specify any crystal structure.

Q. Does the '364 patent disclose information related to the crystal structure of Tapentadol?

A. Yes, it does.

Q. What does it disclose?

A. So, it has a full single crystal x-ray structure determination which gives the, if you like, the entire crystal structure, for want of a better term, the position of the molecules and the way they are packed in the solid. It also discloses the x-ray powder diffraction pattern of form A of

Tapentadol hydrochloride.

Q. Is more than one crystal form -- is there more than one crystal form of Tapentadol?

A. Yes. The disclosure also gives the same kind of information, single crystal structure and powder, as well as other bits of information on the form B of Tapentadol hydrochloride.

Q. And is that referred to as polymorphism when there's more than one crystal form?

A. Yes, that's right. So, these two crystals are polymorphs of one another so the system can be said to be polymorphic.

Q. And what is a polymorph?

A. So, when you have a situation like this in which there are two ways of packing a particular given molecule within three dimensional space, that's polymorphism. It results in the same molecule in two different crystal structures.

Perhaps the better way to think of it is if you think of the molecule as a brick like a house brick, then you can build a wall in more than one different way. You could interleave the bricks together, perhaps get a stronger wall or you can just pile them up in a line and that might be perhaps a weaker wall in terms of the way in which it's built.

Then I suppose if you were to knock the wall down and the bricks all fell into a pile, then that would be analogous

to an amorphous solid.

Q. How does one distinguish one polymorph from another?

A. A wide range of solid state techniques, the ones that I mentioned, the patent of course, the single crystal and powder x-ray crystallography. Other spectroscopic techniques such as infrared and raman spectroscopy. Sometimes even more simple things such as melting points in some cases can distinguish polymorphs.

As I mentioned before, differential scanning calorimetry can be another way to observe a polymorphic phase transition. So know that there's one polymorph transforming into another for example and perhaps measuring melting points through a variety of techniques.

Q. Can you focus on x-ray powder diffraction for a moment? Could you explain briefly how x-ray powder diffraction works?

A. Yes, to put it crudely it's a little bit like a medical x-ray. The x-rays are shone on the crystal. They interact with the internal structure of the crystal and then they are diffracted. They pass through the crystal and they diffracted in a particular way that gives rise to an x-ray powder diffraction pattern which has the appearance of a series of peaks of particular intensities on a horizontal scale which is labeled two theta the diffraction angle.

Q. And are those powder patterns able to identify one polymorph compared to another?

A. Yes, the x-ray powder diffraction pattern is characteristic of the particular crystal packing arrangement. It depends directly on the crystal packing arrangement. And so it's a direct probe of what the internal structure is. And so each polymorph should have a unique x-ray powder diffraction pattern.

Q. Professor Steed, were you in court last week to hear some discussions regarding example 25 of the '737 patent?

A. Yes, I was.

Q. Could I ask you to turn to that patent? It's defendant's trial Exhibit 752. I'd like to direct your attention to example 25.

A. Okay.

Q. Which is up there on the screen.

The procedure for, to make the molecule in example 25, is that actually listed in example 25?

A. Not as specifically. It actually says it's made in the same way as example 24 using the opposite handedness of starting material minus 21.

Q. Example 24 as well, take a look at that. Read all the text of the three steps.

Could you explain just generally what is disclosed in example 24?

A. Yes. So example 24 is a kind of umbrella heading for three separate chemical reactions in which one molecule is

transformed into another molecule and then to another molecule. And ultimately the final product of the third step is a chemical reaction in which Tapentadol the molecule is formed and then it's added to hydrochloride to give Tapentadol hydrochloride which then crystallizes out and at that point the crystal form is determined.

Q. Okay. It's a little hard to see. It goes over several columns.

Have you prepared a demonstrative that sort of summarizes the steps laid out in example 24?

A. Yes. So, I've helped to prepare a demonstrative that lays out the three steps in terms of the chemical transformation also that did occur.

Q. I will put that on the screen now, slide Number 4.

So maybe, could you explain using this demonstrative what exactly, what exactly is shown in these three steps?

A. Yes. So, we've got three quite distinct chemical reaction steps with purification at the end of each one of them.

In the first step, the initial precursor which is the molecule that's shown the top left there which has an OME at the top, ME stands for methyl group and an OH group in the middle, that's transformed into a compound. It's very similar, but in which the OH in the middle has changed into a CL.

THE WITNESS: Perhaps, your Honor, would it be

okay if I point with the laser?

THE COURT: Go right ahead.

Did we get the demonstratives handed out?

MR. HARP: I think so, your Honor.

THE COURT: Did we get them?

MR. HARP: It's rather thin.

THE COURT: Is it in the notebook or is it separate?

MR. HARP: It's separate.

THE COURT: I have it. Thank you.

MR. HARP: We have another one.

THE COURT: No, I'm good. Yes, you may definitely go forward if you'd like to. Would you like to do that?

THE WITNESS: Thank you.

Q. If you'd like to, Professor, that's fine.

A. Yes. So in step one we got the chemical reaction in which this OH here is transformed into a CL. That's using this reagent thionyl chloride. And then we got a second chemical reaction step. So we haven't formed Tapentadol yet.

Step 2 entirely separate step in the reaction in which this chloro that we formed in the first step is then transformed again. It's transformed into hydrogen. So, when chemists write the structure, we don't especially put the hydrogen on. That's something implicit. It's a shorthand way

of drawing it.

And these reagents, sodium borohydride and zinc chloride followed by phosphene, triphenyl phosphene, do that transformation. That gives us this molecule at the end of Step 2 which is the immediate precursor.

And then in Step 3 we finally synthesize the Tapentadol molecule. And all that involves is removing this methyl group, the ME here, using concentrated hydrobromic acid, very strong acid. And then that's neutralized by base, that gives us OH here, and that gives us Tapentadol free base, which is Tapentadol without the hydrochloride.

And then in the final step we add a source of hydrochloric acid, a Tapentadol hydrochloride crystallizes out. And that's the end of Step 3.

Q. At what point in these steps do we actually get the Tapentadol hydrochloride product?

A. It's the very, very last step where we add the hydrogen chloride, the hydrochloric acid, to the Tapentadol that's formed by removing the ME group from the precursor. At that point the Tapentadol hydrochloride crystallizes out.

Q. And what steps are important for making the polymorphic Tapentadol hydrochloride?

A. The polymorph isn't formed until that very, very last step in which there's a crystallization from solution. So until the hydrochloric acid's added right in the very last

step, the Tapentadol molecule is this solution and there's no solid form there.

So that very last step is the only one that's relevant in terms of defining the polymorphic form and of course the conditions under which it occurs.

Q. And what polymorph should result from the synthesis described in example 25?

A. The only polymorph that's stable at room temperature which is form A.

Q. Why is that?

A. Well, there are only two known polymorphs of course. Form A is the one that's stable at room temperature. And unless it's impure, form B transforms into form A at room temperature.

So, we would fully expect to get form A from this reaction unless impurities are somehow stopping the form B from doing that.

THE COURT: You know what, just go back to step 2 for a moment. If we are looking at the ring on the left versus the right, in terms of the stereochemistry, we have a dotted line on the left coming off of the ring and a straight line from the right. If you could explain that to me.

THE WITNESS: Yes, because we are removing this chloro group, the chloro has the highest atomic weight there. And the stereochemistry is assigned based on atomic weight.

And so the chlorides takes priority.

But, when we change the chloro into a hydrogen, obviously a hydrogen has an atomic weight of one so the hydrogen is lowest priority. So the molecule is switched around from chloro having highest priority coming forward to we now put in this diagram this part here which has the highest priority coming forward and the hydrogen is going backwards.

So, in terms of the formalisms of the rules, as Dr. Buschmann alluded to, although he didn't mention atomic weight, the form configuration is inverted, R becomes S, S becomes R, depending upon what terms we are talking about.

THE COURT: Thank you.

Q. Professor Steed, have you reviewed the work of scientists at the University of Wisconsin who reproduced the synthesis described in example 25?

A. Yes, I have.

Q. What was the result of that synthesis?

A. They carried through the Step 3 of example 25. So they carried out the chemical synthesis from the precursor to produce Tapentadol free base. And then they carried out the hydrochloric acid crystallization step to produce Tapentadol in crystalline form. And they actually got a mixture of form A and form B.

Q. Have you reached an opinion as to which form of Tapentadol will result if one follows example 25?

A. In the absence of impurities it will be the form A. The impurities can't stabilize form B.

Q. Let's look a little more closely at what the work that was done at Wisconsin. If you could look to defendant's trial Exhibit 299, please.

A. Okay.

Q. What is this document, defendant's trial Exhibit 299?

A. Yes. So, this is a document produced by the scientists at the University of Wisconsin describing the compound that they began their work with. So, the immediate chemical precursor to Tapentadol. It's the one with the ME group on the ring oxygen.

And so this is the chemical starting material which would produce Tapentadol.

Q. What exactly did the scientists at Wisconsin do to determine the nature of the starting material they were using?

A. Yes, they didn't make this. This was made by other scientists who had carried out a chemical synthesis to get to this point. And then in order to make certain that it was the right compound and it was pure, they carried out a variety of tests, tests that they list here. And I can go through those if you'd like.

Q. Please do.

A. So amongst many tests, for example, they looked at the melting point of the compound. They observed the melting point

of 164 to 165. That's consistent with the compound that they knew about in the literature. And they cite the '593 patent which has the same specification as the '737.

So, 163 to 164 is the literature value. The 164 to 165 is the same within experimental, theh are very close indeed.

Q. Did they conduct any other types of tests to determine the identity of the molecule?

A. Yes, they did. So, they checked the actual molecular structure using hydrogen and carbon NMR, nuclear magnetic resonance spectroscopy.

Q. That up there on that line?

A. Yes. So that's a spectroscopic technique which is done in solution. It doesn't say anything about crystal form. And its job is to check the molecular structure, make certain it's the right number of atoms and they are in the right relationship to one another.

And they can also tell you about organic impurities. And by organic I mean impurities that might contain carbon and hydrogen. The NMR technique looks at specifically hydrogen and carbon. So, any impurity that has hydrogen and carbon in it will show up by NMR. Of course if the impurity doesn't have hydrogen and carbon in it it won't show up.

THE COURT: Could you just explain that a little bit more in terms of it's done in solution. What does that mean?

THE WITNESS: Yes, so they would take the molecule -- it's on the screen. And the precursor molecule in this case but any molecule and literally dissolve in the solvent.

THE COURT: Do you know what the solvent is?

THE WITNESS: It's a bit like dissolving sugar in coffee.

THE COURT: Do you know what the solvent is?

THE WITNESS: Oh, it's the NMR experiment. It's usually something like dimethyl sulfoxide. I'm not sure if they state it here.

Q. You can go back to the other page too.

THE COURT: Is it in the document?

THE WITNESS: I don't see it here.

Q. Professor Steed, if you could go forward to the fifth page of the exhibit, I believe there is --

THE COURT: What page in the exhibit?

MR. HARP: The fifth page in the exhibit.

A. It is here, your Honor. It's a solvent CD3OD that's NMR spectroscopy, the solvent has to be deuterated. So that's actually methanol with the hydrogen atoms in methanol exchange and you have to do that to get a signal in NMR spectroscopy.

THE COURT: Thank you.

Q. If you can go back to the second page of the exhibit.

A. Yes. So, broadly speaking, that's a check for the

identity of the molecule and a check for whether there's any impurities observed.

Q. Why would a chemist want to run these kinds of tests before starting a synthesis, doctor?

A. All chemists like to start with pure starting material so the impurities don't interfere with the final product.

THE COURT: If there were impurities other than hydrogen and carbon, how would they be detected?

THE WITNESS: They wouldn't show up by NMR spectroscopy. They might show up in the melting point. If the melting point was depressed below the literature value, that be a sign of impurities as well.

In terms of impurities of the left and right handed molecules, what I would call enantiomeric impurities, they also measured the optical rotation. And that's this alpha D25 number. They observed a number of minus 25.7 and compared that to the reported number of minus 23.8.

Those numbers are sufficiently similar to reassure me that they have the correct enantiomers. It's another plus number for example.

THE COURT: Now, would that just show the right enantiomers or would it show any type of impurity as well, the optical rotation?

THE WITNESS: It would only show the optical rotation of impurities. So if it was 0, for example, it would

be a 50/50 mixture of the enantiomers.

THE COURT: So, in terms of any other impurities aside from testing for hydrogen and carbon, it would just be the melting point that would demonstrate that? It is usually a low melting point?

THE WITNESS: That's right in terms of the test that they did. But we also have a certificate of analysis on the material, which is an additional test which I could get for you.

Q. Professor Steed, could you maybe scoot a little closer to the microphone?

A. Surely.

Q. Move your chair a little forward if you have room. Thank you.

A. Is that better?

Q. Yes. Thank you.

A. Confounding.

Q. You just mentioned a certificate of analysis.

A. Yes. So, they did their own tests to satisfy themselves first did they have the right stuff and that it was pure. And also they compared their tests to the certificate of analysis that they received with the material which they also include in this document.

Q. Is that at Page 8 of defendant's trial Exhibit 299?

A. Yes. So this is an analytical report which came to

them with the material that they received. And this reports some additional tests further establishing, I think to their satisfaction and to mine, that the material was pure to begin with.

So, for example, and the way to read these analytical reports is there's a column that says test, which is the identity of the test. There's a specification which says what the compliant material should look like under that test. And then the results are given in the right hand column.

So, for example, under the description we find that this was a white powder. That's good evidence that it's free of at least colored impurities, none visible to the naked eye.

THE COURT: So, I'm sorry, so, the certificate itself states that they did which tests? This is when the substance actually came?

THE WITNESS: Yes. So these tests would have been done by analytical scientists producing the material who then sent it to them.

THE COURT: So, outside of the University of Wisconsin?

THE WITNESS: Yes.

THE COURT: Okay. And what test is this reflective of?

THE WITNESS: A whole variety of tests as listed in the test column there. The first one I was referring to

was simply the physical description of the material. Tapentadol hydrochloride is well, Tapentadol hydrochloride but also this compound as well, the white material, and this is indeed says that it is a white powder. So, it's free of at least visual impurities.

Q. What other types of tests were done on this certificate of analysis?

A. Yes, they also checked of solubility, soluble in methanol. We saw that in the NMR spectrum that that's indeed the case. So it complies. The material was identified by IR, that's infrared spectroscopy. That's another technique, looks, it happens to look at vibrations in molecules. But again it gives us a fingerprint of the molecular structure. And also to some extent the solid form, although that's not relevant for this compound because we haven't, it's not even Tapentadol yet.

But, it has a compliant under infrared spectrum. So it has the right kind of bond in it. The analytical report reports the loss on drying. So that's where in this case you heat the material at a high temperature, 105 centigrade for three hours and see whether it loses any mass. So that's a test for volatile impurities.

And we find that it loses very little mass at all. And it loses .35 percent of its mass so that's a very small amount.

There's a residue on emission test. That basically means you burn the stuff. And because it's an organic

molecule, it should all burn away and you shouldn't be left with anything behind, of course, any ash.

If there was that would be a sign of some inorganic impurities. The specification says not more than .2 percent so really quite low. In fact they found 0.03 percent. So, tiny, tiny, minuscule amounts.

Similarly, there's a heavy metals test. Of course this is an organic compound. It shouldn't have any heavy metals in it. The specification says that it shouldn't have more than ten parts per million to be a complaint material. And the results are that it complies. So, it doesn't have more than ten parts per million. So, again, a small amount.

Rather like the Wisconsin scientists themselves, the analytical report also reports optical rotation excess of around enantiomeric impurity. The material complies if it's a negative value between 23 and 27. The specification reports 23.7ish so again it's compliant.

It details a series of tests. I will keep going through them. So, in test eight the analytical report looks at the purity as measured by a number of particular identified impurities using the technique called high performance liquid chromatography, HPLC. That's a technique with its own solution. And it looks at how fast particular molecules and their impurities, for that matter, travel down a chromatography column. So you can identify by how long they spent on it, what

the particular impurity is.

So, that identified two particular impurities what they call the diastereoisomer impurity. And that's present in tiny amounts. And it's within specification.

Similarly, hydroxy impurity should be there and not more than two percent. Actually they're in .05 percent so again as a compliant material. They look at the total unknown impurities. You can't always identify every tiny impurity that's there. Unknown impurities should be not more than .2 percent. Again, we have .09. So very, very low amounts indeed.

There's a specification for total impurities shouldn't be more than three percent, if fact it's .149 percent. So very low total impurities as well.

Q. What are the last two tests that are shown there?

A. More of the same kind of idea. The assay by HPLC based on dry basis involves calculating how much should be there, taking away how much the loss in drying is there. So, the .35 percent. So we had a slightly anomalous result. The assay is 100.3 percent and that's because there is a little bit of loss on drying. But, again, it's within specification. Specification is less than 97 percent.

And the final test is a test for various residual solvents that might be left over from the synthesis. The specification allows certain amounts of each of these solvents.

And in fact the material's well within specification on the two where any solvents were detected and the end is not detected for this.

Q. What did you conclude based on all this analysis of the starting material that was used at Wisconsin?

A. Wisconsin scientists concluded that it was a compliant material suitable for further use and I agree with them. It's very pure material.

Q. At which step in example 25 did the Wisconsin scientists begin their reproduction?

A. So, that matches somewhat what the patent describes as Step 3. It's the last synthesis step followed by the crystallization step.

Q. Is step 3 an appropriate step at which to begin the reproduction of the synthesis described in example 25?

A. Yes. As I said, example 25 consists of three separate syntheses and Step 3 is the last of those syntheses. It's the one that actually makes the Tapentadol molecule and then subsequently crystallizes it as Tapentadol hydrochloride.

So, that's absolutely the place to begin if you are interested in the crystal form of Tapentadol hydrochloride.

Q. I would like to direct you to a defendant's trial Exhibit 298 which is another document from the University of Wisconsin.

Have you seen this document before?

A. Yes, I have.

Q. What is this document?

A. So, similar format. This is then their electronic lab book detailing the actual chemistry that they did on that compound we've been talking about, the precursor compound. So, this is the Step 3 of example 25 of their reproducing.

Q. And have you helped to prepare a demonstrative to show how the work done at the University of Wisconsin prepares for the procedure set forth in example 25?

A. Yes, I have.

Q. Is this that demonstrative?

A. Yes, I have compared step by step all the individual steps, the unit operations, I would call them, within step three of example 25 within that recipe and gone through and made certain that that was done to my satisfaction at the University of Wisconsin work.

Q. Let's start with row Number 1. What's happening in the first step there?

A. So, the diagram there shows us it's the same diagram as was on my previous slide and it shows us the actual chemistry that's occurring. So the OME group is being replaced by an OH group. And along the way we're going from a hydrochloride salt as a precursor minus 23, the reaction of hydrobromic acid and then we end up with a hydrochloride salt of the product Tapentadol hydrochloride.

Q. If we could flip back to DTX 298 and take a look at the description, what they actually did, can you point out for us where they carried out that step?

A. Yes. So, this first step is to dissolve 4.3 grams of that precursor molecule we were talking about in 100 milliliters of concentrated hydrobromic acid. And so they give the chemical name of that precursor we've been talking about. I won't read it out because I don't think even I can do that.

They take that compound. It's the one with the structural formula in the previous exhibit. And they take 4.3 grams of it, as the patent teaches, and they add hydrobromic acid, 48 percent is concentrated and it's a hundred mil. That's what the patent teaches.

Q. So, if you go back to the demonstrative, the Wisconsin scientists faithfully carry out that step?

A. Yes.

Q. What's the next step in the process?

A. So, then it needs to be brought to boiling. The mixture is heated under reflux for two hours. That means boiling that water solution of hydrobromic acid with the precursor in it.

Q. So, if you would flip back to the notebook page, please, do we see that they carried out that step?

A. Yes, mixture was heated to 83 degrees for two hours.

Q. Was that step carried out faithfully?
A. Yep.
Q. So, go back to the demonstrative. How about step Number 3? What's happening in that step?
A. So once that reaction is complete, the reaction mixture is cooled to room temperature and it's concentrated under vacuum.
Q. And go back to the notebook page.
Did they follow that portion of the procedure correctly?
A. Yes, exactly what it says. So the reaction is cooled to RT, that's room temperature, and concentrated in a vacuum.
Q. If we go back to the demonstrative, that was faithfully carried out, step Number 3?
A. Yes.
Q. What's happening with step Number 4?
A. Then at this stage we've got this vast excessive, this very aggressive concentrated hydrobromic acid. So we need to get rid of that, neutralize it. So that's done with a base, concentrated hydrogen carbonate solution. And that's done until an alkaline reaction is obtained.
Q. Was that faithfully, was that step carried out by the scientists at the University of Wisconsin?
A. Yes. So what they say is the residue is neutralized with such with anhydrous sodium hydrogen carbonate in aqueous.

It's in water. And then they give the ph that they got at the end of that process which is a ph of 8. So exactly neutral would be a ph seven. And they have gone beyond ph 7 to 8 which is alkaline as the patent teaches.

Q. We go back to the demonstrative. Okay to put the checkmark in that box?

A. Absolutely

Q. And what about step Number 5?

A. Yes. Then the patent teaches that the resulting mixture which is crude Tapentadol should be extracted twice with 50-milliliters, 2 lots of 50 milliliters of dichloromethane which is an organic solvent.

Q. Was that carried out at Wisconsin?

A. Yes. So, the mixture was extracted with DCM, that's dichloromethane, 50-milliliters times two.

Q. And so check off step number five?

A. You can check that one.

Q. Let's go to the next page.

What happens next in the process, step Number 6.

A. Yes, so then the combined two lots of 50-milliliters of dichloromethane have to be dried and there's a drying agent used to do that, that's sodium sulfate.

Q. And was that done at the University of Wisconsin?

A. Yes. Just as I said, the combined organic phases were dried with anhydrous sodium sulfate.

Q. Okay to check the box on that one as well?
A. Yep.
Q. What's happening in step Number 7?
A. They want to get rid of the solvent dichloromethane so we use a vacuum for that. We distill it off in the vacuum.
Q. Let's go back. Do you see them carrying out that step in their notebook?
A. Yes, they give this lovely phrase concentrated to afford a crude tedious oil. I'm sure it was a tedious procedure. And then it was dried in a vacuum to remove the dichloromethane just as the patent teaches.
Q. Very good. Go back to the demonstrative and check the box. You agree it's appropriate to check the box for step number 7?
A. Yes.
Q. And what about step Number 8?
A. We are left with crude Tapentadol. It's dissolved, the patent uses the words taken up, that means dissolved in another organic solvent to butanone.
Q. Was that carried out at Wisconsin as well?
A. Yes, the crude residue from the evaporation is taken up in butanone and that gives the amount.
Q. Go back to the demonstrative. Step Number 8 faithfully carried out by Wisconsin?
A. Yes.

Q. What's the next step in the process?

A. Then we come to the final step which is where we go from the butanone solution of Tapentadol free base to Tapentadol hydrochloride. So we have to add the source of hydrochloric acid.

In this case it's done by premixing a source of hydrochloric acid, so trimethyl chlorosilane with water. And mixing those two together generates hydrochloric acid which can then react with the Tapentadol to give Tapentadol hydrochloride.

And the idea is that the Tapentadol hydrochloride is not soluble in the butanone and so it crystallizes out and then we get crystal product.

Q. Is it important that the trimethyl chlorosilane and water are premixed?

A. Yes, the chemical reaction between the trimethyl chlorosilane and the water generates the hydrochloric acid. So that reaction needs to occur to give you the hydrochloric acid before you can add it to the Tapentadol. Otherwise you could get side reactions occurring.

Q. Let's look at what the scientists at the University of Wisconsin did.

Can you explain how they carried out that step?

A. Yes, so they took a premixed mixture which they describe as a biphase mixture of TMSCL that trimethylsilyl

chloride, a different name for the same thing. They give the amounts and water in a 1 to 1 ratio in terms of numbers of molecules or mini mols as they put there.

It was added and they say a white solid precipitated immediately so they got the crystal occurring as the patent teaches.

Q. If we go back to the demonstrative, please.

A. Yes. So you can put the tick there.

Q. Was it significant to you that the scientists reported that they saw white powder as soon as they added the TMCS and water mixture?

A. That's certainly what I expect because Tapentadol hydrochloride is insoluble in butanone. And more importantly it's what the patent teaches. So at that point the patent says that the product crystallizes out and that's the end of the procedure.

So, the fact that that worked for them means that the chemistry worked for them, that they carried out a successful reproduction.

Q. What was the final product that the scientists at the University of Wisconsin obtained?

A. Yes, they report it as a white powder which of course it should be.

Q. How did the scientists at Wisconsin know what they had actually made?

A. Yes, so then rather like they did on the starting material they then carried out the similar kinds of tests in order to characterize their product. So they carried out hydrogen and carbon NMR spectroscopy, for example, to the melting point.

THE COURT: I just have a follow-up question with respect to the starting material but I'm going to address this to counsel because it may actually be something that's protected.

Do we know where the starting material is obtained from? And if it is something that needs to be protected, we will seal the courtroom later just to get that answered.

MR. HARP: I don't think it needs to be sealed.

THE COURT: All right.

MR. HARP: If we go back to the notebook page, it's from Norac. It's a company called Norac.

THE COURT: You know what, let's ask, should we ask the witness? That's okay.

Do you know where the starting material came from?

THE WITNESS: Yes, your Honor.

THE COURT: All right. Where did it come from?

THE WITNESS: As Counsel said the Wisconsin scientists actually note in their lab book that it comes from Norac Pharma.

MR. HARP: I think that's in defendant's trial

Exhibit 299.

THE COURT: 299?

MR. HARP: Yes, under preparation.

THE COURT: What's document number on that?

MR. HARP: DTX 299, Page 2.

THE COURT: All right. And the company, I'm sorry, that performed the certificate of analysis prior to doing the work at Wisconsin, what was the name of that company?

THE WITNESS: The name that's actually on the analysis, I understand, is a supplier to Norac. But, I don't know the details of how these companies are related. It's exhibit D, I believe.

THE COURT: I'm sorry, exhibit D to which document?

THE WITNESS: Exhibit D to, I'm sorry, to my report.

MR. HARP: It's defendant's trial Exhibit 299.

THE COURT: 299. So, it's the same document. Do you know the page on that?

MR. HARP: Eight.

THE COURT: Thank you.

Q. So, if we could go back to Exhibit 298, please.

So what did the scientists at the University of Wisconsin determine when they tested their product using NMR?

A. Yes. So, they give the spectrum but they also give --

yes, so they performed proton and hydrocarbon NMR spectra. Actually the solvent mixture, methanol and dimethyl sulfoxide. They give the NMR spectrum there and it corresponds to the right product as far as I am concerned.

Q. So, when you say the right product, what is that they made?

A. Tapentadol.

Q. They made Tapentadol. Did they characterize the polymorph of the material that they made?

A. Yes. So they also sent the sample to an x-ray powder diffraction laboratory.

Q. If we go to defendant's trial Exhibit 297, please, have you seen this document before?

A. Yes, I have.

Q. And what is this document?

A. Yes. So, this is the experimental details of the x-ray powder diffraction measurements. And Page 3 of this document actually has the powder pattern on it.

Q. Let's take a look at that pattern on Page 3. Are we looking at it here on the screen?

A. So, this is an x-ray powder diffraction pattern measured on the sample that they made and it shows that the sample is a mixture of form A and form B Tapentadol hydrochloride.

Q. How have you been able to determine that the sample

contains form A?

A. It has all the peaks that are identified as being form A peaks within the '364 patent.

Q. And what peaks are those specifically that you're looking at?

A. So, the ones that are most obvious to me are the peaks at 18.9 and 22.5 which are quite unique peaks for form A. But I've checked into that and it actually has all the peaks listed in claims 1 and 2 of the '364 patent.

Q. Let's take a look at those claims. Defendant's trial Exhibit 304. If we take a look at claims 1 and 2. Are those the peaks that you identified in the powder pattern for the Wisconsin project?

A. Yes, they are both listed, both claims 1 and 2

Q. Are all those peaks present in the pattern for the Wisconsin project?

A. Yes, they are.

Q. Did you consider the intensities of the peaks when you compared the Wisconsin pattern to the peaks listed in the claims.

A. Only insofar that they were consistent with what I would expect given this is a mixed sample. But, in comparing the two claims, I looked at the peak positions with the area that the patent gives which is plus or minus two in two theta.

Q. Is there a figure in the '364 patent that contains the

powder pattern for form A?

A. Yes, that's Figure 1.

Q. Take a look at that. Did you compare Figure 1 in the '364 patent to the pattern obtained by the University of Wisconsin?

A. Yes I did, and the University of Wisconsin data is consistent with Figure 1 albeit also with the presence of form B as well.

Q. So, how does the pattern for the Wisconsin product compare to Figure 1?

A. It's essentially the same thing.

Q. Has it been disputed that the Wisconsin product contains form A of Tapentadol hydrochloride?

A. No, it hasn't. Dr. Bernstein in his report also said that form A Tapentadol hydrochloride is present.

Q. Professor Steed, were you in court last week to hear Grunenthal's witnesses discuss samples they said resulted in form B at room temperature?

A. Yes, I was.

Q. Do recall what those samples were?

A. What they were. You mean in terms of their code numbers? I believe it's the charge 0 you are referring to. And also Miss Mueller's reproductions of this procedure?

Q. Right, right. There was also some discussion of Dr. Buschmann's batch one. Do you remember that?

A. Yes.

Q. You didn't list that one in your answer. Why didn't you list that one?

A. No powder diffraction data had been provided on that sample to me.

Q. So, let's talk first about Miss Mueller's attempt to reproduce example 25.

Have you reviewed the notebooks documenting her work?

A. Yes, I have.

Q. Having reviewed those notebooks do you have an opinion about whether her work was a faithful reproduction of example 25?

A. No. I don't think it was a faithful reproduction quite simply the procedure just didn't work in her hands. She didn't get a product where the patent says she should, in any of her reproductions.

Q. Can you say it in a little more detail what do you mean she didn't get what the patent describes?

A. Yes, so that very last step of the patent, the point which the Tapentadol hydrochloride crystallizes out, in her hands, when following the teachings of the patent, nothing crystallized out. The procedure just quite simply didn't work.

Q. Was there anything else about the product that she eventually did obtain that indicated to you that the reproduction hadn't worked properly?

A. Yes, well, when she finally did get a product out by cooling it in an icebox for 90 minutes then she got what she described as a mustard yellow compound which, as all chemists will tell you, is a pretty bad sign in terms of purity.

Q. Do you know who Miss Mueller is?

A. I am not acquainted with her personally.

Q. Do you know what her job was at Grunenthal or is at Grunenthal?

A. Yes. I have reviewed her background from her deposition transcript. It's my understanding she was a technician working in the process development labs with expertise in analysis.

Q. Do you know how much experience Miss Mueller had with the synthesis of Tapentadol at the time she did her reproductions of example 25?

A. She stated it was the first time she was ever doing the reaction, ever handling Tapentadol.

Q. How many times did Miss Mueller attempt to follow example 25?

A. I think initially she did three reactions and then a rather later one, I think much later around 2009.

Q. Let's take a look at some of her notebook documenting her attempts. If you could turn to defendant's trial Exhibit 1003.

Have you seen this document before?

A. Yes, I have.
Q. What is this document?
A. So, this is an English translation of Miss Mueller's notebooks from her attempt to reproduce the example 25.
Q. If I could direct your attention to pages 14 and 15 of DTX 1003.
A. Okay.
Q. Have you seen those pages before?
A. Yes, I have.
Q. What was documented on those pages?
A. So, these two pages are, on the left, Page 14 is her first attempt to reproduce example 25. And the Page 15 is her third attempt to reproduce example 25.
Q. Okay. And have you reviewed the work that's documented on these pages?
A. Yes, I have.
Q. How does the work that Miss Mueller performed here correspond to example 25 in the '737 patent?
A. It deviates from it in a number of quite significant ways. And as I alluded to the fact that at the end the patent just didn't work, the point she should have gotten crystals, she didn't get anything, so clearly it didn't work for her.
Q. What were the mistakes that she made?
A. There's several of them. I have prepared a demonstrative which might make it a little bit more helpful.

Q. Why don't we take a look at that. I think it's slide Number 9.

A. So, this demonstrative compares the areas where she made mistakes compared to the same steps that I went through with the University of Wisconsin work.

So, in looking at this the first thing I noticed was that she said that she had never actually characterized the starting material that she used, that precursor molecule with the OME group on it, she said in her deposition that she didn't characterize it. I don't know why.

I also noted she didn't start with the amount that the patent teaches. She used 4.55 grams instead of 4.3 for some reason.

Q. Let's take a look at her deposition testimony. It's DTX 285. It's Page 60, lines 15 through 19. Is that also testimony that you were referring to in your answer?

A. Yes.

Q. So, what didn't she do here?

A. So, she was asked if she examined the purity of the 35111 chemical product. The 351 is the immediate chemical precursor. It's her code for the immediate chemical precursor of Tapentadol. It's the compound that we were talking about in the Wisconsin context.

She was asked if she examined the purity of that starting compound and she said no.

Q. Thank you. Let's go back to the demonstrative please.

So what conclusions did you reach about whether Miss Mueller faithfully carried out the first step in example 25?

A. So, in terms of the starting material that she was working with, we don't know whether it was pure or not. She didn't carry out those tests and she didn't start with the amount that the patent recommends.

Q. Are there any other mistakes that she made in the process of attempting the reproduce example 25?

A. Yes, then she carried out a similar process to the Wisconsin scientists until we get to Step 4. This is the step in which that very, very strong hydrobromic acid needs to be neutralized.

If it isn't properly neutralized then it can carry through into the final product. This is the step where we can kill it off. The patent teaches that it should be neutralized until an alkaline reaction was obtained.

Q. If we look back to her notebook page in DTX 1003 at Page 14, if you could blow up starting there. Actually it's above the paragraph above that.

Can you point out here where she is describing work that she did related to that step?

A. Yes. So, she does say she rendered the residue alkaline, rendered the residue alkaline. It's concentrated sodium hydrogen carbonate solution, but she doesn't say what ph

that went to. So that just creates a little doubt in my mind. If she just went to just alkaline ph 7.01 it may not be enough to properly kill off the hydrobromic acid.

Q. Why would that matter?

A. Well, this is our chance to destroy the hydrobromic acid and make it back into sodium bromide in this case but remove it from the reaction.

And so if it isn't destroyed at this point, then it can carry through to the final product. This is the stage at which it gets neutralized.

Q. What other mistakes did Miss Mueller make?

A. Yes. If we go back to the demonstrative.

Q. Sure.

A. Yes. So, I just want to focus on Step 5 there. Can we just get up to -- so, Step 5 is the extraction with two lots of 50 milliliters of dichloromethane. I wanted to show you what that looks like.

So if you go to the next demonstrative, the way in which is that's done is a manual process. It's done with this piece of apparatus, a separating funnel. The dichloromethane layer and the crude alkaline layer that contains all the impurities, as well as the Tapentadol free base at this stage are mixed together and they form two layers like this within our funnel.

It's the operator's job basically to open the tap, run

the two layers through, and close the tap at the point where they decide, in this case the water will be on the bottom because it's full of salt. When the water is finished going through and the organic solvent is entering the tap, then they have to quickly shut the tap off, switch the flask over and then collect the organic layer and do that twice.

What happens then, what always happens is that there's lots and lots of droplets of water in the dichloromethane. So you always get a very wet solution there. So that's why it's important to dry it. And that's Step 6.

Q. Why does it matter that there could be water left in the aqueous phase?

A. Remember we need concentrated hydrobromic acid and we neutralized it with sodium carbonate. So the water is full of sodium bromide. It's a very, very concentrated solution of sodium bromide. And so this is our chance to get rid of it in the water layer. And if don't remove all the droplets of water, the sodium bromide in the droplets of water will carry through.

Q. How is the water removed?

A. That's through use of the drying agent. What the patent teaches is that the combined organic phases, that's the two lots of 50 milliliters of dichloromethane, were dried over sodium sulfate.

Q. And if we go back to Miss Mueller's notebook pages and

DTX 1003, Page 14.

A. Yes, so she does something that's actually slightly different and significant. So, she says that she filtered the extract over sodium sulfate. There's a big difference between filter over and dry over.

So, when you dry something over a drying agent, what you do is you place the drying agent into the flask, you swirl it around a bit then let it sit for 5 or 10 minutes to absorb all the moisture.

If you filter over it, what you're doing is you're pouring the dichloromethane over the drying agent and it filters straight through. So, the contact time is far, far less. That means it's not going to be dried properly.

Q. And what could be the result of the failure to dry the aqueous phases properly?

A. Droplets of water passing through into the final product which are laced with impurities, particularly sodium bromide. But also any other trace impurities that have been generated in this very aggressive reaction. It's very concentrated acid.

Q. Did she make any other mistakes in the process? If we go back to demonstrative.

A. Yes. The final one I identified was right at the very last step, that's the step at which the polymorphic form was identified, the Tapentadol hydrochloride.

The patent teaches to add this premixed mixture of trimethyl chloro silane and water at which point the product crystallizes out. That's not what she did, however.

Q. Can we go to the notebook. What did Miss Mueller actually do?

A. So, first of all she added the water directly to the butanone solution of the Tapentadol free base. And then she added separately the trimethyl chloro silane again directly to that butanone solution.

Q. So she didn't premix those two reagents. Is that right?

A. No, she didn't give them a chance to react together to produce hydrochloric acid. So instead the trimethyl chloro silane can react with the Tapentadol. There's a risk of at the point of addition you suddenly get generation of HCL which causes degradation byproducts and so on. It's just generally not what the patent teaches in this prior practice.

Q. Just to be clear, what effect would it have on the reaction to not have done the premixing?

A. It's another way in which it would generate impurities.

Q. What happened in Miss Mueller's experiment after she added the, sequentially added the TCMS and water?

A. Nothing. No crystals came out.

Q. Is that significant to you?

A. Yes. The patent teaches that after addition of TMCS

water mixture, the Tapentadol crystallizes out. If it doesn't crystallize out, then the patent hasn't worked. The procedure hasn't been followed properly.

Q. Let's go back to the notebook. What did she do when she didn't obtain crystals?

A. Then she tried to get the crystals to come out by improvising. And so she immersed the rest of the entire reaction mixture, the butanone reaction mixture in an ice bath, set it for 90 minutes, and then she did get a solid coming out.

Q. What was the net results of all these mistakes?

A. She did ultimately isolate a low yield of product. And unfortunately it was a yellow product. She described it as mustard yellow. So a really unpleasant, discolored looking impure product.

Q. And Professor Steed, just to backup a little bit, this experiment we've been talking about is, if we go to the top of the page, does she have a label for this product? For the final product that was given a code labeling, a number. Do you know what that was?

A. Yes. And I think you are highlighting it. The 351 is the starting compound and the product label is 322. So BU 322. Now, having heard Dr. Buschmann's testimony, I understand what the 11 means, reaction method one and sample one.

Q. If you go to Page 15 of this document, DTX 1003, what's on this next page?

A. So, this is her third attempt to reproduce it. I think she abandoned her second attempt. And this is the same procedure except that now she used just a one third scale so instead of starting with 4.3 grams of starting material, she began with 1.23 grams and she scaled the amount of hydrobromic acid down as well.

Q. And did she, did Miss Mueller make mistakes in her third attempt here for GBBU 322-1-3?

A. Yes, she made exactly the same mistake she made the first time around. I think she obviously got something out the first time so she did it again exactly the same way because that's the way it worked for her. The procedure is essentially identical to repetition one.

Q. What in the end was the net result of the product that she got on this page?

A. Again a discolored product she described it as beige.

Q. If we could flip back one page as well. I would just like to -- where on the Page 14 of DTX 1003 does she report the color of her product?

A. This is not her page. This is repetition one. That's mustard colored.

Q. I'm sorry. I've gone back to repetition one.

A. I'm sorry.

Q. I'm backing up. Sorry to be confusion.

A. Yes. So it's right at the bottom there under the

heeding appearance on repetition one.

Q. And what was the appearance of the final product?

A. It was mustard colored in repetition one.

Q. Do you recall a later attempt by Miss Mueller to reproduce example 25?

A. Yes, I believe she did a third attempt at reproduction in 2009.

Q. Could I ask you to turn to defendant's trial Exhibit 1034, please?

Have you seen this document before?

A. Yes.

Q. What is this document?

A. This is again an English translation of her lab book from that fourth reproduction.

Q. And does this attempt faithfully follow example 25?

A. No. This is a completely different reaction because she's not starting with the right starting material. So under reactions, she starts with BU 351 hydrobromide salt. So, the patent teaches start with hydrochloride salt. So this is a different chemical substance.

Q. What were the -- did she make any other mistakes in this process as well?

A. She did this process in much the same way she had done repetitions 1 and 3. So, for example, with the sequential addition of the trimethyl chloro silane and the water.

Q. And what was the product, if we go to the next page, what was, actually two pages to Page 3 of the exhibit, what was the result of all those mistakes?

A. Yes. So, in this case she obtained a cream colored solid.

Q. What does that indicate?

A. So again it should be white. So again this colored impurities, there it's a discolored product.

Q. Professor Steed, are you also aware of some work done at Grunenthal, some other work -- sorry, strike that.

Professor Steed, are you aware of any other work done at Grunenthal that plaintiffs allege results in form B at room temperature?

A. The only other work that I'm aware of is Dr. Buschmann's charge 0.

Q. Have you reviewed the lab notebook describing the synthesis for charge 0?

A. I have, yes.

Q. Could we ask you to turn to defendant's trial Exhibit 974, please?

Have you reviewed the document?

A. Yes.

Q. What is this document?

A. This is the English translation of Dr. Buschmann's lab book from that charge 0 reaction.

Q. Is the synthesis described in exhibit 974 the same as example 25?

A. No, it's completely different. So, he never does that Step 3 we've been talking about. He carries out a chemical reaction from a different molecule. It's a chloro molecule. If perhaps if I point with a laser pointer, is that okay, your Honor?

THE COURT: That's fine.

THE WITNESS: Thanks.

Q. So, it starts with the chloro molecule CL here. That's not the starting material for Step 3. He carries out this step with a triphenylphosphine reaction to give the Tapentadol molecule it's hydrochloride.

So this isn't the hydrobromide reaction at all. It's completely a different chemical reaction with a completely different starting material.

Q. Were you in the courtroom during Dr. Buschmann's testimony?

A. Yes.

Q. And did his testimony confirm that batch 0 did not follow example 25?

A. Yes, it did.

Q. What's the chemical purity on the batch 0 product?

A. Dr. Buschmann, I believe, carried out some tests. I believe he carried out an NMR spectroscopy and he looked at the

melting point.

The melting point is quite strange. It's what's labeled as F.P. here. And he says that it sinters at 123 degrees C with decomposition. And the melting point of Tapentadol hydrochloride is 200 degrees C. So way, way different from 123.

Q. So, is there an actual melting point reported in DTX 974?

A. No, no melting point. The sintering process, the compound remains a solid during sintering. It's a kind of merging together of particles.

Q. So what's the difference between the sintering point and the melting point?

A. So there's no actual melting. No liquid is formed here. And as I said, he noted the decomposition and it's a very, very different temperature. So, this indicates to me, well, it's hard to know what to make of it. It certainly isn't a good melting point indicating a high purity product. It seems to be indicating something that's very impure indeed.

Q. Have you reviewed the synthesis of Dr. Buschmann's batch one?

A. Yes.

Q. Let's look, if I can ask you to turn to DTX 977. Do you recognize this document?

A. Yes, I do.

Q. What's described on this notebook page?

A. So, this is his notebook page in English translation for so called charge one, his second, his second synthesis of Tapentadol.

Q. Is this method the same as the method that was used to make batch 0?

A. No. This method much more closely parallels example 25. So this is a reaction of the example 25 precursor, the methoxy compound with hydrobromic acid to get Tapentadol hydrochloride.

Q. Have you seen any x-ray theta for batch one?

A. No.

Q. Even if they didn't follow example 25, how do you explain the results of Miss Mueller and Dr. Buschmann seeing some form B that persisted at room temperature?

A. These are both highly impure samples. Those impurities can prevent the normally unstable form B transforming to form A. So these are not Tapentadol hydrochloride but actually mixtures of Tapentadol hydrochloride with other impurities sufficient to stop it from transforming to the normally, the only stable form of -- the only form of Tapentadol that's stable at room temperature.

Q. What evidence have you seen that form A is the stable form at room temperature and that form B converts to form A at that temperature?

A. The evidence is abundant. So, in particular I can point to a single crystal x-ray crystallography in which form B transforms to form A above room temperature. Powder x-ray diffraction was looked at and showed that form A is the only form stable at room temperature. And differential scanning calorimetry also shows that form A is the only form stable at room temperature.

Q. Let's talk about the powder x-ray diffraction studies you mentioned. If we look at the '364 patent which is defendant's Exhibit 304, column 18.

A. Okay.

Q. Is this the variable temperature x-ray diffraction data that you were talking about?

A. Yes. This is the description of the experiment.

Q. What are they doing in these experiments?

A. Yes, so very simple. All they are doing is recording the x-ray powder diffraction pattern. I think they started at around 30 actually in the actual data but at a lowish temperature. They recorded as form A.

Then they are heating the sample and recording the x-ray powder diffraction pattern. Every time they heat it, I don't know what steps they are going through but probably just a few degrees.

And what they say is that form A converts to Form B between about 40 and 50 degrees centigrade.

Q. And what happens next after they've done the heating step?

A. So, then the x-ray powder pattern for form A changes to the Form B powder pattern above the transition temperature. And then they cool the sample down, they get the same sample. Monitor the x-ray powder diffraction again and B transforms back into A again.

Q. And what does that -- what conclusion do you draw from that experiment?

A. It's what we scientists call an enantiotropic pair. So one form is stable at room temperature; one form is stable at high temperature. And there's a very fast conversion between them such as you see that conversion happening on the time scale of the experiment. So a matter of a few minutes.

So, In other words, form B simply doesn't persist at room temperature. It's unstable.

Q. You also mentioned some single crystal x-ray studies that showed this behavior.

Could we take a look at defendant's trial Exhibit 993, please. Can you go to the next page?

What is this document?

A. Yes, this is a report sent to Grunenthal Dr. Gruss by Professor Englert at the University of Aachen detailing his single x-ray diffraction studies on Tapentadol. What Dr. Englert found was that if he took just one single crystal of

form A and determined its structure, he was able to find the crystal packing arrangement, the shape of the molecule and of course a single crystal experiment allows you to directly calculate the powder pattern. The two are related to each other.

He unambiguously identified form A at room temperature. And what he did was to warm it up to the transition point and I believe he found in his crystal it was 48 centigrade. And he watched that one single crystal transform into form B. And then he did a full single crystal x-ray structure examination on form B.

And then what he found was that when he cooled it down again, that one form B crystal transformed into form A again.

Q. So what did Dr. Englert conclude about the behavior of form A and form B?

A. He was actually able to realize that the only difference between form A and form B, they are very closely related. The only difference is a very small rotation of one of the organic groups. And perhaps we could put up the picture that he has on Page 2 of his document. Right. That picture there. Thank you.

So, the form A molecule, if I may point again, is this one on the left. And if you look at this little organic group, just here it's and ether group, that's the form A shape. And when he did the x-ray structure of Form B, having warmed it up,

that little organic group just laid over on its side right back.

So, that small twist is the only difference forms A and B. And what Professor Englert was able to do was to calculate that these two different shapes were essentially the same as each other. And he calculated the barrier interconversion between them which he found was five kilocalories per mol, which is a very low energy barrier indeed. The kind of energy that is just around in the atmosphere, the transition temperature of 30 to 40 in this case.

So, he was able to show that it was a very small transition between the two crystal structures. It was a very easy transition. It didn't involve breaking or making any bonds. And so it wasn't surprising that it would happen so readily and so form B would transform back to A as soon as you cool it.

Q. Is it fair to say that the transition between A and B is reversible?

A. Absolutely.

Q. And what is the third piece of evidence you mentioned showing that forms A and B interconvert?

A. Yes, that's a differential scanning calorimetry. So, I think this is a technique that Dr. Gruss talked about. It's a technique in which the heat taken in by a sample or given out by a sample relative to a reference is measured as a function

of temperature.

So you warm the sample up. See if it takes or gives out any heat which might indicate a phase change. And then cool it down again, see if it takes or gives out heat again that might indicate it transforming from one form to another.

Perhaps the simplest analogy is something like melting. So if you take ice which is a stable form at low temperature and put heat in, it will transform to water which is the stable form at the higher temperature above the melting point.

THE COURT: Sorry, what is the third figure did you say on this?

THE WITNESS: It's the third figure. I didn't mention a third figure. Oh, sorry, it's the superposition of the two.

THE COURT: Of one over the other?

THE WITNESS: Yes.

THE COURT: Go ahead. I'm sorry.

A. So the DS experiment basically allows you to look at phase changes like one polymorph to another or like melting. It allows you to look by virtue of heat that goes in or comes out during the transformation.

Q. If I could ask you to take a look at defendant's trial Exhibit 1243, Page 9 of that document.

Have you seen this document before?

A. Yes, I have.

Q. What is it?

A. So, these are a series of slides produced by Grunenthal's Dr. Andreas Fischer who is inventor of the '364 patent in 2005 which summarizes Grunenthal's understanding of polymorphism of CG 5503 Tapentadol hydrochloride.

Q. And on Page 9 of this document, what are we going to see on this slide?

A. Yes. So, these are two DSC scans, differential scanning calorimetry scans showing the transformation of form A into Form B.

Q. Can you briefly walk us through the experiment and tell us what's happening with the data on this page?

A. Yeah, I would be happy to. So, and if I may point again, so if you look at the horizontal scale, it's pretty hard to make out, but this is temperature and degree centigrade with room temperature on the left here going up to a little over 200 on the right here which is beyond the melting point.

And probably the best place to start is on the upper trace. I'm just on the horizontal section here. So, once the sample in reference to underneath the equilibrium, get rid of this here, this horizontal line means that no heat is going into or leaving the sample as we raise the temperature going on the line until we get to the beginning of this peak just here.

And this peak is pointing upwards. It's what we call an endotherm. It means that the heat is taken in by the sample

and that heat is required to drive this transformation of form A to form B.

So, as we increase the temperature through this peak, the sample takes in heat. That allows form A to transform to form B and eventually on the other side of the peak the sample is now all form B so the peak dies away again.

We then carry on with essentially a horizontal line all the way up in temperature until this enormous great peak which is around 200 centigrade and that's the melting of Tapentadol. You can see how much bigger a peak melting is in the phase transformation. The phase transformation is a very small heat indeed because it's a very easy transformation.

Q. What's happening on the lower trace that we see on the page?

A. Then we have the reverse experiment, the cooling down experiment. So, if we start around 40 degrees, see here at the transition point, this is where the sample is form B. And then as we go horizontally from right to left cooling down, we see a downward pointing peak, opposite direction of the other peak. That's where the heat that went in to make form A into form B is now coming out again as form B transforms back into form A.

And the beginning of this peak is around 24 and a half degrees centigrade. And so by the time we've gotten to room temperature, the sample is transformed all the way back to form A. And that's the end of the experiment.

Q. Does the DSC provide information about how quickly this transformation happens between A and B?

A. Yes. So, a typical heating arrangement of DSC will be around ten degrees C per minute. And so if we just look at the width of that cooling peak for example there, the width of that peak is around ten degrees C ballpark. So, this process is occurring in under a minute.

Q. Based on the data that we've just been talking about, how do you know that the Grunenthal reproductions must have impurities?

A. Well, we see it here that if you've got a sample of Tapentadol, then it will transform from form B to Form A by the time you get to room temperature. And so if that doesn't happen, there must be something stopping it.

We can see the behavior of Tapentadol. It's form A stable at room temperature thermodynamically. Form B is only stable at high temperature, not just thermodynamically, but also form B is kinetically unstable.

What that means is the rate of transformation, B back to A, is fast. When you cool down. And we can see that directly from the DSC here. It occurs within a minute.

So if that's happening with this sample of Tapentadol hydrochloride, then if you see a sample that's persisting at room temperature, we know that Tapentadol hydrochloride is both thermodynamically and kinetically unstable at room temperature.

So there must be an impurity stopping it from transforming. There has to be.

Q. Did you help prepare some demonstratives that illustrate the behavior you're talking about?

A. Yes, I did, just cartoon fashion. So, the best way to think it about it as an analogy is that in position A, form A if you think of Tapentadol hydrochloride as being like a spring, then when it's coiled up it's stable. That's the room temperature stable form.

When you warm it up to position B, heat goes in that allows the spring to stretch out into an unstable state. And then it would naturally spring back again which is the reverse peak going backwards in the DSC.

The only thing that would stop it from doing that is if some impurity gets in the way and literally physically prevents that transition from occurring. And I've represented that in cartoon fashion just with the pencils getting in the way. I don't know if you've got that slide.

So the stretch spring represents form B. And as you cool it down, it becomes unstable. We know it should transform back to Form A fast. But if something gets in the way, the impurities, that can stop it and make it metastable. In other words, make it long lived at room temperature even though it's not thermodynically stable.

Q. Was Grunenthal aware of the role impurities play in

stabilizing form B at room temperature?

A. Yes, they were. They discussed it extensively.

Q. Can we look at DTX 1243 at Page 18.

How do you know that Grunenthal was aware of the role of impurities?

A. Yes. So, just looking at this slide on Page 18, this is a slide in which they recognize that in some special cases polymorph B was obtained and does seem to be stable at room temperature, flying in the face of their own DSC data.

And they recognize that this was a special case and an anomaly and they tried to explain it. And they came up with four possible explanations.

One is impurity profile. They recognize that impurities might simply stop the form B transforming if it wasn't pure enough. They also considered the possibility of particle size. But there's another slide in this document in which they rule that out by systematic study of particle size and transition temperature and conclude that there is no effect.

They also consider the possibility of mixed crystal formation which is also impurities, specifically where the impurities are actually getting into the intimate crystal structure of the crystal and preventing it from transforming. So 1 and 3 are both impurities.

And they also wondered whether they might even have a

new polymorph. But, there's only forms A and B of Tapentadol known up until now at least anyway.

Q. Does this document include any studies of a particular impurity profile?

A. Yes, it does.

Q. Where do you see that, sir?

A. On the very next page. Page 19.

Q. Page 19 of defendant's trial Exhibit 1243?

A. Yes, so this refers to a series of batches of Tapentadol hydrochloride with the label CEPM which Grunenthal prepared by recrystallization in order to try and eliminate impurities.

And so batch CEPM one is a recrystallization batch in which the Tapentadol hydrochloride is dissolved in a solvent. It's cooled and crystallizes. I forget what the solvent was. I am not sure about that. It crystallizes out to form A and the form A crystals are filtered off and removed.

And yes, in fact, we can see from the table that it's modification A that comes out in batch CPM one because it's been recrystallized and the impurities have been removed.

What they then did was with the liquid that's left over from filtering off those form A crystals, they then evaporated that liquid. They got rid of the organic solvent and looked at what solid was left behind.

Now of course this is a crystallization. The idea is

that the form A crystallizes out and leaves behind the impurities and solution. And so if you then evaporate that solution, of course what you've got left behind is remaining Tapentadol hydrochloride and all the impurities.

That's what we are seeing here. So batch CEPM 1 A is the impurities, is impurities that were left behind from the CEPM 1 crystallization. They analyze specifically three different impurities. They've given the code name shown there. And you can see that there's almost three percent of impurity 300, .32 of impurity 210, and 351 at 1.88 percent and that comes out as modification B.

So, you can compare those two numbers. CPM one has very, very low levels of impurities of those three particular impurities. CPM 1 A has much higher levels. CPM 1 B, CPM 1A as B impurities are stabilizing to form B.

Q. Were new conclusions reached regarding the role of impurities according to this document?

A. Yes. It was the same exercise for CPM 2 and 2A. Again the impure one was B. The pure one was A. And even CPM 3 and 3A, CPM 3A a little bit less impure and it was a mixture .

And what Grunenthal scientists said was as it says that impurities effect the formation of the unfavored modification, form B.

Q. Does this document address any other types of impurities?

A. This particular document doesn't address any other kinds of impurities. But normally impurities tend to flock together. So while this document only analyzes specifically for three particular impurities, generally impurities in a recrystallization like this, all the impurities left behind in the mother liquor as it's called. So even if they weren't analyzed for them, there may be other impurities present as well.

Q. Is there any study of an inorganic impurity that's represented in another slide in this document?

A. Yes, Grunenthal scientists were worried particularly about bromide.

Q. If you could turn to Page 21 of DTX 1243.

A. Yes. So they specifically considered the possibility that bromide, which is chemically very, very similar to chloride as in Tapentadol hydrochloride, could substitute for chloride within the hydrochloride lattice.

Because Bromide is only very slightly bigger than chloride. It's right adjacent to it on the periodic table and has very similar chemistry and of course is involved in the synthesis reaction, they were worried that bromide might get into the crystals and cause this retardation effect.

They likened the effect to the doping the semi conductors where an impurity gets into the semi conductor structure and actually changes it's properties.

Q. What is meant by in the second bullet point here?

A. Yes. Well they noticed that, I only have this bullet point to go on, but they must have actually characterized the bromide salt of Tapentadol hydrochloride. And what they say is that the corresponding bromide salt has an isotypic structure, in other words has the same crystal structure as form B.

So it's not surprising that bromide could substitute for chloride within the form B crystal structure.

Q. Are you aware of any other documents that discussed the role of impurities in stabilizing form B.

A. Yes, there are a number of other documents that Grunenthal talks about impurities stabilizing form B.

Q. If I could ask you to turn to defendant's trial exhibit 995. Have you seen this document before?

A. Yes, I have.

Q. Does the document address the role of impurities in stabilizing form B?

A. Yes. So this is a document, it's a report on crystallization studies undertaken by a company Crystallics and it's addressed to Dr. Gruss from Grunenthal. They have a specific section on impurities within the document. I believe it's on page Bates number ending in ten at Page 10 of the document.

Q. It's defendant's trial Exhibit 995 Page 10.

A. Yes. So, in the first paragraph there.

Q. What's described in this section of the document?

A. So, Crystallics says that Grunenthal has previously indicated that the polymorphic form of CG 5503, Tapentadol hydrochloride, is affected by the amount of the impurities. That was the instruction that got particularly with regard to two impurities which they've identified by code names here, present in the mixture upon crystallization.

And what Crystallics did was then to try and decide what the effects of those two impurities were on whether form B persists or was formed at all. So they did a particular design of experiments in which, in which they carried out systematic experiments to try and see whether those two particular impurities would influence the polymorphic form.

Q. What conclusions did they reach? I think it's on the next paragraph down.

A. Thank you.

Q. Blow that up.

A. Yes. And so it's the second sentence. The second paragraph. Yes. So, they concluded after that systematic study that higher amounts of GRT 0912Y, which is an impurity, were observed to have a larger influence of the formation of polymorph B than GRT4045Y gather impurities that they were asked to look at.

Q. Are you aware of any other Grunenthal documents that discuss the role of impurities in stabilizing form B.

A. Yes, I am.

Q. Could I ask you to turn to DTX 1008 in your book? Have you seen this document before?

A. Yes, I have.

Q. What is this document?

A. So this is another Grunenthal internal report and discussing their for polymorph investigations on Tapentadol hydrochloride.

Q. Does this document address the role of impurities in stabilizing form B?

A. Yes, it does. It's on the third page of the document.

Q. What does this document say about impurities?

A. So, this is within the context of these anomalous room temperature long lived form Bs. They say that in a bullet point, in three bullet points they make three different attempts to explain the behavior.

One, do they have contamination with bromide in the sample to give a co-crystallization that occurs to decrease the DSC transition point? In other words make the B to A transition occur below room temperature. Do they have other impurities like byproducts of degradation products that effect the transition temperature. Or is there a third polymorph modification present and that doesn't seem to be the case.

So, the first two again refer to either bromide is an impurity or degradation product impurities.

Q. What do you conclude based on these Grunenthal documents about the discussion in all these Grunenthal documents about impurities?

A. It's quite clear that if form B persists at room temperature, it's impure. Impurities are stabilizing the form B otherwise it would transform to form A at room temperature. It seems Grunenthal was well aware of this problem and I agree with their speculations.

Q. Based on all the information you have reviewed in this case, does example 25 inherently anticipate the asserted claims of the '364 patent?

A. Yes, it does.

Q. Professor Steed, I'm going to move ahead a little bit to streamline some of the questions. And I want to direct your attention to PTX, plaintiff's trial Exhibit 1547.

Were you in the Court last week for testimony related to the XRPD pattern for Dr. Buschmann's batch 0?

A. Yes.

Q. Do you recognize this document PTX 1547?

A. I do.

Q. What is this document?

A. Yes. So, I believe the blue trace is Dr. Buschmann's, said by plaintiffs to be Dr. Buschmann's batch 0. And the red trace is what they used as a reference material which is a powder diffraction pattern, I hasten to add.

And the red trace is the powder diffraction pattern of the reference material CEPM 1A that's the compound I was talking about which results from evaporating the mother liquor from the form A crystallization which is CPM 1. And so this is a very impure batch indeed which is form B.

Q. So, what is the impurity content of CEPM1A?

A. That was the impurities that we looked at on the table a few minutes ago and analyzed the three specific impurities identified by code name which were present in amounts of around 2.8ish percent, point 3 percent and 1 and a halfish percent I think.

Q. What is the red trace on PTX 1547?

A. So the red trace is what we are talking about, that's CPM1A. That's the impure reference material.

Q. What's the blue trace?

A. The blue trace is said by Grunenthal to be the powder diffraction pattern of Dr. Buscmann's batch 0.

Q. What's the impurity content of Dr. Buschmann's batch 0?

A. We know from its lack of melting point it's sintering point, that it must be very impure.

Q. Professor Steed, do you have an opinion as to whether or not the '364 patent is obvious?

A. Yes I believe it is obvious.

Q. And how do you come to that determination?

A. All it reports is the only form of Tapentadol

hydrochloride which is stable at room temperature. So, any crystallization experiments on tapentadol hydrochloride would straightaway reveal form A with all of its characteristics.

Q. Could I ask you to take a look at the '364 patent again? Please. It's defendant's trial Exhibit 304. If you could look at the first page?

A. Okay.

Q. What's the filing date of the '364 patent?

A. It dates from June 28, 2004.

Q. And what is the level of ordinary skill with respect to the subject matter disclosed in the '364 patent as of that filing date?

A. Person of ordinary skill would be somebody with perhaps a Ph.D. in chemistry or subject like crystallography and crystallization science or perhaps somebody with a lower degree but some years of industrial research or laboratory experience.

Q. Can I direct you to the '737 patent which we were talking about earlier today. That's the one with example 25. That's DTX 752.

A. Okay.

Q. Does the '737 patent disclose the synthesis of Tapentadol?

A. Yes, this is at example 25.

Q. Do you have an understanding as to why Grunenthal was making Tapentadol and the other molecules that are disclosed in

the '737 patent?

A. Yes. They wanted to use them as medicines for pain and analgesics.

Q. If I could direct you to column one of the '737 patent. How do you know that this project was aimed at finding analgesics?

A. Yes, I think that's under the heading summary of the invention. The patentee says the underlying object of the present invention was to provide substances with an analgesic effect which is suitable for the treatment of severe pain.

Q. Thank you.

Q. Does example 25 identify the crystal structure of the Tapentadol product?

A. No, it doesn't. Just that it can be made in crystalline form.

Q. Would a person of skill be motivated to find out if there was more than one crystal structure of Tapentadol?

A. Yes, absolutely. Screening for crystal forms is a routine part of the business of pharmaceutical companies.

Q. And why is it a routine part of the business?

A. Well, amongst other things because the FDA requires them to carry out a polymorphism screen and decide whether or not polymorphism is relevant to the performance of a drug substance and therefore whether they need to control for it.

Q. Could I ask you to take a look at defendant's trial

Exhibit 290. Have you seen this document before?

A. Yes.

Q. What is it?

A. So these are the FDA guidelines with supporting documentation in drug applications as of February 1987.

Q. And are these the FDA guidelines you were mentioning in your answer a moment ago?

A. Yes, among a number of documents.

Q. So, where in this document is the FDA telling drug developers about polymorphism?

A. They have a specific section on polymorphism. You may have to help me with the page number.

Q. Go to Page 37 of the document.

A. Thank you. Yes, they have a specific heading entitled polymorphism.

Q. Actually on Page 36.

A. Yes. The section starts on 36 and runs to 37.

Q. Right.

A. So, perhaps the most appropriate place to look is the middle of Page 37 where the FDA says approximate analytical procedures should be used to determine whether or not polymorphism occurs.

So, In other words, carry it out a screen for polymorphism and determine if the drug substance is polymorphic. And then it gives examples of the analytical

procedures that can be used to analyze the results of that screen for whether they have the same or different crystal forms.

Q. Would a person of skill in the art have understood as of June 2004 how to conduct such a polymorph screen?

A. Yes absolutely.

Q. Are there publications that provide guidance on how to do such a screen?

A. There certainly are.

Q. Could I ask you to turn to DTX 755 please. Do you see that document?

A. Yes.

Q. What is that? What is DTX 755?

A. This is a review article written Dr. Steven Byrn and his colleagues which talks about the FDA's requirement to carry out a polymorphism screen and then make a decision as to whether the resulting polymorphs that have or haven't been discovered are relevant to the formulation of the drug substance in its long term stability and so.

Q. Can you direct us to the portion of the document that describes what you just talked about?

A. Yes, so the very first paragraph after the abstract discusses this issue. So it says Interest in the subject of pharmaceutical solids stems in part of the Food and Drug Administration drug substance guideline that states appropriate

analytical procedures should be used to detect polymorphic hydrated or amorphous forms of the drug substance.

Q. Does this paper go on to describe how to carry out an investigation to determine polymorphism?

A. Yes. This paper describes what it calls a strategic approach. So a systematic well defined approach to satisfy the FDA's guidelines requirements.

Q. Where do we find that in the paper?

A. So, the best place to look is in Figure 1 which is a decision tree covering how to screen for polymorphs and then decide if they are relevant to the production of the drug substance.

Q. And how does one carry out such a screen?

A. Yes. So very simply the decision tree begins with the question, have polymorphs been discovered. So that's the polymorph screen. And it gives guidance as to how we can answer that question, whether polymorphs have been discovered or not.

So, the paper teaches that we can discover polymorphs if they exist by carrying out a range of different recrystallization experiments using different solvents with different polarity. The kind of standards that would be known in the lab. And systematically vary the temperature, the concentration, whether or not there was agitation and the PH and so on, simple routine trial and error experiments, changing

the conditions to see what crystallizes.

Q. Does the Byrn paper identify particular solvents that should be used?

A. Yes, it gives an exemplary list of particular common solvents that would be good starting points to try. That's in the second column on the same page under the heading A formation of polymorphs. Have polymorphs been discovered?

So Dr. Byrn suggests that the suitable starting point of solvents would include water, methanol, ethanol, propanol, isopropanol acetane, cetanol triethyl acetate, hexane and mixtures.

Q. Are you aware of the polymorphs screen that Grunenthal conducted on Tapentadol?

A. Yes, I am.

Q. Who conducted that polymorph screen?

A. They contacted an external research company SSCI to do the polymorph screen.

Q. Have you seen any documents describing that project?

A. Yes, I have seen the final report from SSCI describing in detail the polymorph screen they conducted.

Q. Turn to DTX 2001, sorry 1001. What is DTX 1001?

A. Yes. So this is the final report from SSCI of the polymorphism screen on Tapentadol hydrochloride that they carried out in 2001 for Grunenthal.

Q. How did SSCI carry out the screen?

A. They did essentially what Dr. Byrn instructs. So they carried out a variety of different crystallization of Tapentadol hydrochloride in a variety of different solvents under a variety of conditions

Q. Are those results gathered somewhere in this document?

A. Yes, Table 3 of the document give the results of the polymorph screen.

Q. That's on Page 14 of DTX 1001?

A. Yes. And it goes onto Page 15 as well.

Q. What were the results of these screening experiments?

A. Yes. So you see in the left hand column the different solvents that they chose, the conditions, they varied the conditions, fast evaporation, slow evaporation, slow cooling and slurrying experiments.

They give a sample number and then they analyze the results by x-ray powder diffraction. And in every single case where they got a solid material, they got form A.

Q. Did SSCI use any of the solvents that Dr. Byrn suggested in the paper we were looking at a moment ago?

A. Yes, with the exemption of water they used every single one of them.

Q. What polymorph was found in those experiments?

A. A every time.

Q. Is it surprising to you that form A appears in all of the results where crystals were obtained?

A. Not at all. Form A is the only form that's stable at room temperature. So I would have been surprised if they hadn't found it.

Q. If you could turn quickly to the claims of the '364 patent. That's DTX 304.

Professor Steed, what do claims 1, 2 and 3 of the '364 patent cover?

A. They cover crystalline form A Tapentadol hydrochloride, the one that was discovered in all of these polymorphism screens including the experiments and they identified by its powder diffraction peaks and the overall appearance of its powder diffraction pattern.

Q. Would the polymorph screen described in Byrn have found that Form A -- would have found the form A polymorph of Tapentadol?

A. Yes. The powder diffraction pattern of a particular organic substance is directly related to its internal structure. So, if you crystallize a particular organic substance and do its powder x-ray diffractogram, then you'll find its characteristic peak positions and it's overall peak appearance. And so for Form A Tapentadol this is what it would look like.

Q. Let me direct your attention to claim 25 of the '364 patent, please. What does this claim cover?

A. This claim is directed to a solid form as a

pharmaceutical composition comprised as an active ingredient crystalline form A of Tapentadol hydrochloride. Again recognized by the same peaks that are listed in claim one.

Q. Would it have been obvious to a person of skill to use form A Tapentadol in a pharmaceutical dosage form?

A. Yes absolutely.

Q. Why?

A. Form A is the only form that's stable at room temperature. So the commonsense reason is you wouldn't want to use a form which might then transform into form A and therefore mean your medicine is unstable.

Q. Are you aware of any guidance in the literature that would support your conclusion?

A. Yes.

Q. Turn to DTX 930. What is DTX 930?

A. This is an article by Sherry Morissette and her co-workers talking about particular polymorphism screen techniques published in 2004.

Q. Does the Morissette paper discuss using thermodynamically stable polymorphs in dosage forms?

A. Yes, it does on Page 2 of the document, the first column. So, what she says is that the preferred solid form is generally the thermodynamically most stable form of the compound.

Q. Do you agree with that statement?

A. Yes, absolutely. That's the obvious place to start for commonsense reasons. And it's the place where the pharmaceutical industry starts as their first choice for medicine.

Q. How many polymorphs exist for Tapentadol?

A. Just two.

Q. And what kinds of techniques were used to determine the polymorphic forms of Tapentadol?

A. By crystallization for a variety of solvents and then a characterization by a technique like x-ray crystallography.

Q. And the crystallization techniques that were used, are those standard and routine procedures?

A. Yes absolutely. The way we work in this field is by empirical testing. So we just take the substance crystallize it for a variety of solvents in a variety of conditions quite straightforward experiments and analyze the crystals to see what's formed.

Q. Does it matter whether one uses form A or form B Tapentadol in a dosage form?

A. Actually no. As it turns out it doesn't. They are the bio equivalent.

Q. Based on all the information you've reviewed in this case, are the claims of the '364 patent obvious?

A. Yes.

Q. Thank you, Professor Steed. That's all my question.

THE COURT: Thank you. Thank you. All right.

Let's hear from the plaintiffs. I'm assuming no one else is going to be questioning on behalf of the defendants of this witness, correct ?

MR.FITZPATRICK: No, your Honor.

THE COURT: Okay. Let's hear from the plaintiffs on cross. Would you like to put this on for the morning?

MS. RANNEY: That's what I was going to talk about, tomorrow morning. Plaintiffs have over an hour 15 minutes of cross-examination. So, we are thinking it would probably be better to just go tomorrow.

THE COURT: Any issue?

MR. ALY: Your Honor, if I may, we did truncate the direct a bit so maybe we could, as a compromise, leave the direct open if there is a maximum of 10 or 15 minutes of information we need to build on here, obviously not consulting with the expert.

MS. RANNEY: That's fine, your Honor.

THE COURT: You are saying just in case you have a few follow-up questions, you have some opportunity to continue with direct because you tried to really make it quite compact at the end.

There's no issue with that, is there? Any issue? Anyone?

MS. RANNEY: No issue.

THE COURT: That's fine. So you can determine whether you need to do anything further on direct. We will address that first thing in the morning. And then we will deal with the cross in the morning as well thereafter.

Just so we have some idea as to what we have going on, we will obviously be finishing with our witness tomorrow. What else for tomorrow?

MR. SCHULER: Then I believe the next witness is Dr. Martin.

MR.FITZPATRICK: Martin, Stephen Martin.

THE COURT: He will be testifying in what area?

MR.FITZPATRICK: He will be testifying regarding invalidity, your Honor, of '593.

MR. SCHULER: Dr. Metzger will be testifying about the invalidity of the '364 and unenforceability of the '364 patent.

THE COURT: Okay. That sounds like it will probably take care of the day.

MR. FITZPATRICK: I think that will probably fill the day tomorrow.

THE COURT: I could be wrong. You might be quick with them.

MR.FITZPATRICK: No, I think you're probably right.

THE COURT: So, we will have those two witnesses

tomorrow. I think at this point let me release the doctor from the stand.

Thank you very much. You are released. We will see you tomorrow morning at, shall we do 8:30 tomorrow morning?

MS. RANNEY: Your Honor, if you don't mind, could you just give the witness the same instruction given to the other witnesses about not speaking with Counsel?

THE COURT: I will definitely do that.

I do remind you that you are under oath and you're continuing your testimony. So, do not speak with Counsel regarding your testimony and you will be back tomorrow morning to continue it. All right.

What time are we planning?

MR.FITZPATRICK: Can we start at 9 tomorrow, your Honor?

THE COURT: That's fine. Do you want to do 9?

MR. ALY: Yes.

THE COURT: Everyone, 9 o'clock. Nine o'clock tomorrow morning we are beginning.

And so the witness is now excused for the evening. Thank you very much. We will see you tomorrow morning.

Any other cleanup issue that we have to tend to before we depart tonight? Anything else?

MR.FITZPATRICK: None for defense, your Honor.

THE COURT: Nothing. Anything from the

plaintiffs?

MS. RANNEY: No, your Honor.

THE COURT: All right. Sounds good. I think we have our schedule set. So, I will see you tomorrow morning at 9 o'clock. Thank you.

MS. RANNEY: Thank you, your Honor.

(Whereupon the matter was concluded)